1433774

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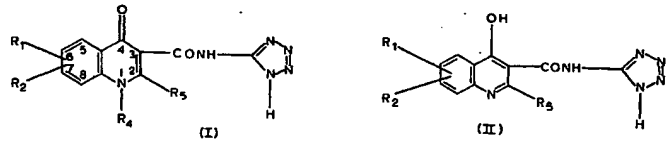
(54) HETEROCYCLIC COMPOUNDS

(71) We ALLEN & HANBURYS LIMITED, a British Company of Three Colts Lane, Bethnal Green, London, E.2, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel quinoline-3-carboxamidotetrazole derivatives, to processes for the production thereof, to pharmaceutical compositions containing them and to the use thereof in therapy.

We have found that certain quinoline-3-carboxamidotetrazoles have useful pharmacological activity and in particular inhibit the release of spasmogenic substances arising as a consequence of antigen-antibody reactions.

Accordingly the present invention provides compounds of the general formula (I) below and when (R_4=H) tautomers thereof of formula (II):



In the above formulae:

R_1 and R_2 which may be the same or different represent a hydrogen atom, or a halogen atom, or an alkyl, trifluoromethyl, or nitro group; or a group OR_3 in which R_3 may be a hydrogen atom, or an alkenyl or alkyl group which alkyl group may be substituted by alkoxy, aryl, amino, alkylamino, dialkylamino, hydroxy or acyloxy groups; or a group $—NR_6R_7$ in which R_6 and R_7 may be the same or different and represent a hydrogen atom or an alkyl group which alkyl group may be substituted with a hydroxy or acyloxy group or in which R_6 and R_7 together with the nitrogen atom may form a ring of 5 or 6 atoms which may contain additional hetero atoms, e.g. morpholino, pyrrolidinyl, piperazinyl, N-methylpiperazinyl.

R_4 represents a hydrogen atom, an alkenyl or alkyl group which alkyl group may be substituted by hydroxy, acyloxy, alkoxy, aryl, amino, alkylamino, dialkylamino or alkylaralkylamino groups.

R_5 represents a hydrogen atom or an alkyl group.

The term alkyl when used above to define a single group or a substituent in a group means a straight or branched chain alkyl group containing from 1 to 6 carbon atoms preferably 1 to 4 carbon atoms. The term alkenyl means a straight or branched alkenyl group containing from 2 to 6 carbon atoms, preferably 3 to 5 carbon atoms.

The term alkoxy when used above to define a single group or a substituent in a group preferably means a group containing 1 to 6 carbon atoms, advantageously 1 to 4 carbon atoms.

The term acyloxy as used herein preferably means the residue of an alkanoic acid, preferably a C_{1-4} alkanoic acid in particular formic, acetic or propionic.

Aryl preferably means phenyl and aralkyl preferably means benzyl.

The invention also includes pharmaceutically acceptable salts of the above compounds.

Preferred salts may be those with alkali metals e.g. sodium, or with organic bases e.g. dimethylaminoethanol. Where basic groups are present the invention also covers addition salts with organic or inorganic acids.

When R_4=H the compounds (I) may exist in tautomeric equilibrium with structures of formula (II) and the latter are also understood to fall within the scope of the invention.

Preferred classes of compounds are those in which the following groups have the meanings given:

R_1 and R_2 represent hydrogen, halogen particularly chlorine and fluorine, alkyl particularly isopropyl and butyl, trifluoromethyl, nitro, hydroxy, C_{1-4} alkoxy particularly methoxy, ethoxy and isopropoxy, alkenyloxy particularly allyloxy, hydroxyalkoxy particularly 2-hydroxyethoxy, alkoxyalkoxy particularly 2-methoxyethoxy, aralkoxy particularly benzyloxy, dialkylaminoalkoxy particularly 2-(dimethylamino)-ethoxy, aminoalkoxy particularly 2-aminoethoxy, amino, aralkylamino particularly benzylamino, hydroxyalkylamino particularly 2-hydroxyethylamino, dialkylamino particularly dimethylamino, a heterocyclic group, in particular morpholino or N-methylpiperazinyl or piperidino;

R_4 represents hydrogen, alkyl particularly methyl, ethyl, propyl and isopropyl, aralkyl particularly benzyl, alkenyl particularly allyl, hydroxyalkyl particularly 2-hydroxyethyl, acyloxyalkyl, particularly 2-formyloxyethyl, alkoxyalkyl particularly 2-methoxyethyl, alkylaminoalkyl particularly 2-(methylamino)ethyl, dialkylaminoalkyl particularly 2-(dimethylamino)ethyl, or alkylaralkylaminoalkyl particularly 2-(methylbenzylamino)ethyl; and

R_5 represents hydrogen or alkyl particularly methyl.

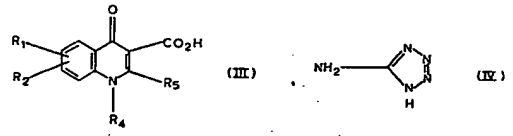
The compounds of the invention show promise as agents for the treatment of conditions in which combination of an antigen with a reaginic antibody is primarily responsible, for example extrinsic asthma, hay fever, urticaria, eczema or atopic dermatitis.

Thus 1 - ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide (Example 11(1)) was found to be 80 times more active than disodium cromoglycate in inhibiting release of histamine in the peritoneal passive anaphylaxis (PPA) test using the DNP-egg albumen system in rats. (J. Exp. Med., 1968, *127*, 767).

The invention also provides pharmaceutical compositions which contain a compound of general formula (I) or a salt thereof either *per se* or when made by a process according to the invention together with a pharmaceutically acceptable carrier or diluent including excipients and other formulatory agents. The compositions may also contain supplementary medicinal agents, e.g. bronchodilators. Suitable forms of oral administration include tablets, capsules, syrups, or emulsions. For administration by inhalation the compositions according to the invention may be in the form of a powder or snuff or as an aerosol spray presentation. The latter may conveniently be a pressurised pack with a metering valve to deliver a fixed dosage unit or may be an aqueous solution delivered via a nebuliser.

The dosage at which the active ingredient is administered may vary within a wide range, depending on the age, weight and condition of the patient. A suitable oral dosage range is generally from 2—1500 mg and for inhalation is from 0.1—20 mg. The dose may be repeated as required.

The compounds according to the invention may be prepared by the condensation of a 1,4-dihydro-4-oxo-3-quinolinecarboxylic acid of formula (III), wherein R_1, R_2, R_4 and R_5 have the meanings stated above or are convertible thereto, or an activated derivative of such acid, with 5-aminotetrazole (IV):



A variety of reagents and conditions may be used to effect this condensation. For example, the condensation may be carried out with the aid of the condensing agents which have found a general application in peptide chemistry. One such reagent, N,N'-carbonyldiimidazole is particularly useful and with this reagent the condensation is preferably carried out in an aprotic solvent such as tetrahydrofuran and/or dimethylformamide, and if desired the reaction may be carried out with heating, e.g. between 50—120°.

In place of the acid (III) one may use an activated derivative thereof such as an acid halide or a mixed anhydride which will condense more readily with 5-aminotetrazole. The reaction with the acid halide is preferably carried out in an aprotic solvent such as dimethylformamide or in an aqueous medium and in the presence of an inorganic base, e.g. an alkali metal carbonate or bicarbonate, or a tertiary organic base e.g. triethylamine. When the condensation is carried out using a mixed anhydride the reaction is preferably carried out in an aprotic solvent, such as dimethylformamide. A particularly useful class of mixed anhydride for this condensation is that derived from the acid (III) and an alkyl or aralkyl carbonic acid, e.g. ethylcarbonic acid (C_2H_5OCOOH).

Compounds according to the invention may also be made from other compounds of the invention by alteration of the groups R_1—R_5 within the meanings given.

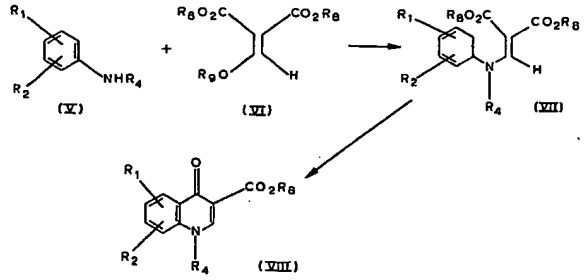
Thus compounds of the general formula (I) in which R_1 represents an alkoxy group OR_8 or the amino group NR_6R_7 in the 7 position may be prepared from the corresponding 7-fluoro derivative by a nucleophilic displacement reaction. The alkoxy derivatives (I: R_1=7—OR_8) may conveniently be prepared by heating the fluoro derivative, I: R_1=7—F) with an alkoxide XOR_8 where X is a metal atom, in particular an alkali metal atom; this reaction is preferably carried out in the presence of a solvent and a particularly useful solvent is the corresponding alcohol R_8OH. Similarly, the amino derivative (I: R_1=7—NR_6R_7) may conveniently be prepared by heating the fluoro derivative (I: R_1=7—F) with the appropriate amine NHR_6R_7.

Also, for example, compounds of formula (I) in which the R_4=$CH_2C_6H_5$ and/or R_1=$OCH_2C_6H_5$ or $NR_6CH_2C_6H_5$ may be converted into the corresponding components in which R_4=H and/or R_1=OH or NHR_6, by hydrogenolysis in the presence of a noble metal catalyst e.g. palladium. Similarly, compounds in which R_1=NO_2 may be converted into compounds in which R_1=NH_2 by catalytic reduction e.g. using hydrogen and a noble metal catalyst such as palladium.

Compounds in which R_4=acyloxyalkyl may be converted into compounds in which R_4=hydroxyalkyl by hydrolysis, preferably with aqueous alkali, in particular, sodium or potassium hydroxide.

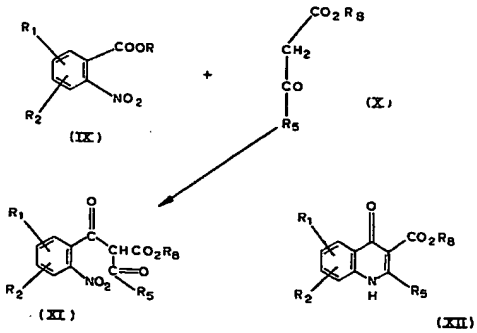
The starting 1,4-dihydro-4-oxo-3-quinoline carboxylic acids (III) are either known compounds or may be prepared by the standard processes of quinoline chemistry.

One such route, the Gould Jacobs synthesis, which is applicable to the synthesis of acids (III) in which R_5=H, is outlined below (Elderfield, Heterocyclic Chemistry, John Wiley, 1952, *4*, 38)



R_8 and R_9 are alkyl groups.

The conversion of the amino ester (VII) into the quinoline ester (VIII) may be achieved by heating in a high boiling solvent e.g. diphenyl ether. Hydrolysis of the quinoline ester (VIII) with aqueous alkali gives the corresponding acid (III; R_5=H). Alternatively, (VII) may be converted directly into the acid (III; R_5=H) by heating with polyphosphoric acid. Alternatively, the acids (III, R_4=H) and the corresponding esters (XII) may be prepared by the reaction schematically set out below and which is described by R. J. Coutts and D. G. Wibberley J. Chem. Soc. 1962, 2578.



This process is particularly applicable to the production of compounds in which R_5 may be alkyl. The conversion of compound (XI) into the ester (XII) may be effected by heating under reflux with palladium on charcoal in the presence of cyclohexene. The corresponding acid (III, R_4=H) may be obtained by hydrolysis of the ester (XII) in the usual way.

The groups R_1—R_5 may be present throughout the synthesis of the compound (III) or may be introduced or modified at any convenient stage. For example, the esters (VIII and XII) where R_1 and/or R_2 are hydroxy groups may be converted into compounds where R_1 and/or R_2 have the meanings OR_3 already given by treatment with conventional alkylating (or acylating) agents for example R_3Y (Y=halogen, R_3SO_4 etc.). In the same way the esters (VIII and XII) (R_4=hydrogen) are converted into compounds where R_4 has other meanings given above using the reagent R_4Y. This reaction may advantageously be carried out at reflux in a solvent such as 2-butanone and in the presence of an alkali metal carbonate such as potassium carbonate.

The mixed anhydrides derived from the acid (III) may be prepared in the conventional manner. For example, a suitable acid halide e.g. ethyl chloroformate is added to a mixture of the acid (III) and a tertiary organic base such as triethylamine, in a polar aprotic solvent such as dimethylformamide. Preferably the reaction is carried out in the cold e.g. between −10 to 10°C.

The acid halide derivatives of the acid (III) in which R_4 has the meanings given other than hydrogen may be prepared from the acid (III) in the conventional manner e.g. reaction with thionyl chloride or PCl_5.

The following Examples illustrate the invention.

Examples 10—24 describe the production of compounds according to the invention. Examples 1 to 9 describe the production of intermediates used in Examples 10 to 24. Example 25 is an Example of a composition according to the invention.

EXAMPLE 1

(1) 6-Butyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, ethyl ester

4-Butylaniline (20.0 g) and diethyl ethoxymethylenemalonate (29.2 g) were heated together on a steam bath for 1 hour. The resulting oil was added to boiling diphenyl ether (200 ml) and the mixture was heated under reflux for 12 minutes and allowed to cool. The solid which crystallised was collected and recrystallised from ethanol, m.p. 254.5—257°, 43%.

In a similar manner were prepared:

(2) 1,4-Dihydro-6-methoxy-4-oxo-3-quinolinecarboxylic acid, ethyl ester, m.p. 273—276° from p-anisidine.

(3) 1,4-Dihydro-6-isopropyl-4-oxo-3-quinolinecarboxylic acid, ethyl ester m.p. 260—262° from p-isopropylaniline 85%.

EXAMPLE 2

(1) 1,4-Dihydro-1(2-hydroxyethyl)-4-oxo-3-quinolinecarboxylic acid, ethyl ester

Bromoethanol (9.8 g) was added to a stirred mixture of 1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, ethyl ester (5 g.) and anhydrous potassium carbonate (15.9 g) in 2-butanone (500 ml). The mixture was heated under reflux for 22 hours and the solid filtered off. The filtrate was cooled and the precipitated white solid was filtered off and crystallised from methanol, m.p. 174.5—176.5°, 49%.

The following compounds were prepared in a similar manner:

(2) 1-Allyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, ethyl ester, m.p. 104—105.5°; alkylating agent allyl bromide, 80%.

(3) 1-(2-Dimethylaminoethyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, ethyl ester, obtained as an oil that did not crystallise; alkylating agent dimethylaminoethyl chloride.

(4) 1-Benzyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, ethyl ester, m.p. 174—177°; alkylating agent benzyl bromide, 71%.

(5) 6-Butyl-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, ethyl ester—an oil that did not crystallise; alkylating agent butyl bromide.

(6) 1-Ethyl-1,4-dihydro-4-oxo-7-trifluoromethyl-3-quinolinecarboxylic acid, ethyl ester, m.p. 142—144°; alkylating agent ethyl bromide, 40%.

(7) 1,4-Dihydro-1-(2-methoxyethyl)-4-oxo-3-quinolinecarboxylic acid, ethyl ester, m.p. 125—127°; alkylating agent 2-methoxyethyl bromide.

(8) 1-(2-Benzylmethylaminoethyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, ethyl ester; alkylating agent 2-benzylmethylaminoethyl bromide.

(9) 1,4-Dihydro-1-isopropyl-4-oxo-3-quinolinecarboxylic acid, ethyl ester, m.p. 187—190°; alkylating agent isopropyl bromide.

(10) 1-Ethyl-1,4-dihydro-6-methoxy-4-oxo-3-quinolinecarboxylic acid, ethyl ester, m.p. 150.5—152.5°; alkylating agent diethyl sulphate.

(11) 1-Ethyl-1,4-dihydro-7-methoxy-4-oxo-3-quinolinecarboxylic acid, ethyl ester, m.p. 111—113°; alkylating agent diethyl sulphate.

(12) 1-Ethyl-1,4-dihydro-6-isopropyl-4-oxo-3-quinolinecarboxylic acid ethyl ester, m.p. 103—105°; alkylating agent ethyl iodide.

EXAMPLE 3

1-Ethyl-7-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, ethyl ester

7-Fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, ethyl ester (80 g), ethyl iodide (107.2 g) and potassium carbonate (110 g.) in dimethylformamide (1600 ml) were heated at 100° for 17 hours. Further ethyl iodide (53.6 g) was added and heating was continued for 8 hours. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was extracted with ethyl acetate in a Soxhlet apparatus. The extract was cooled and the product was collected and crystallised from a mixture of methanol and ether. It has m.p. 107—108.5°.

EXAMPLE 4

(1) 6-Butyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

6-Butyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, ethyl ester (Example 1(1)) (3.2 g), aqueous sodium hydroxide (30 ml., 2N) and ethanol (40 ml) were heated under reflux for 8 hours. The hot solution was treated with glacial acetic acid and the solid that separated was filtered off, washed with water and dried, m.p. above 210° (d), 94%.

The following compound was similarly prepared:

(2) 1,4-Dihydro-6-methoxy-4-oxo-3-quinolinecarboxylic acid, m.p. 259—262°, from ester of Example 1(2).

EXAMPLE 5

(1) 1,4-Dihydro-1(2-hydroxyethyl)-4-oxo-3-quinolinecarboxylic acid

1,4-Dihydro-1(2-hydroxyethyl)-4-oxo-3-quinolinecarboxylic acid, ethyl ester (Example 2(1)) (3.5 g) was added to a solution of sodium hydroxide (0.6 g) in water (30 ml) and ethanol (50 ml) and the mixture was heated under reflux for 30 minutes. One half of the solvent was distilled off and the residue acidified with glacial acetic acid and cooled. The solid was filtered off, m.p. 269—270.5°, 91%.

The following acids were prepared in a similar manner from their ethyl esters:

(2) 1-Allyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, m.p. 209—211° from the ester of Example 2(2), 96%.

(3) 1-Benzyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, m.p. 231—235° from the ester of Example 2(4), 79%.
(4) 1,4-Dihydro-1(2-dimethylaminoethyl)-4-oxo-3-quinolinecarboxylic acid, isolated as its hydrochloride, monohydrate, m.p. 273—275.5° from the ester of Example 2(3), 28%.
(5) 1-Ethyl-1,4-dihydro-4-oxo-7-trifluoromethyl-3-quinolinecarboxylic acid, m.p. 215—218° from the ester of Example 2(6), 90%.
(6) 6-Butyl-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, m.p. 153—154° from the ester of Example 2(5), 69%.
(7) 1,4-Dihydro-1-isopropyl-4-oxo-3-quinolinecarboxylic acid, m.p. 187—190° from the ester of Example 2(9).
(8) 1-Ethyl-7-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, m.p. 310—311° from the ester of Example 3.
(9) 1-[2-(Benzylmethylamino)ethyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, hydrochloride, m.p. 222.5° (d) from the ester of Example 2(8).
(10) 1,4-Dihydro-1(2-methoxyethyl)-4-oxo-3-quinolinecarboxylic acid, m.p. 192—193°, 45%, from the ester of Example 2(7).
(11) 1-Ethyl-1,4-dihydro-6-isopropyl-4-oxo-3-quinolinecarboxylic acid m.p. 193—195°, 56%, from the ester of Example 2(12).

EXAMPLE 6

1,4-Dihydro-6-hydroxy-4-oxo-3-quinolinecarboxylic acid

1,4-Dihydro-6-methoxy-4-oxo-3-quinolinecarboxylic acid, ethyl ester (Example 1(2)) (30.0 g) and aqueous hydriodic acid (225 ml., 55%) were stirred and heated under reflux in a Dean and Stark apparatus, under an atmosphere of nitrogen, for 2 hours. The mixture was cooled and the precipitated solid was collected and recrystallised from water, m.p. 295—297.5°, 76%.

EXAMPLE 7

(1) 1-Ethyl-1,4-dihydro-6-hydroxy-4-oxo-3-quinolinecarboxylic acid

1-Ethyl-1,4-dihydro-6-methoxy-4-oxo-3-quinolinecarboxylic acid, ethyl ester (Example 2(10)) (8.8 g) and aqueous hydriodic acid (80 ml., 55%) were heated under reflux in a nitrogen atmosphere in a Dean and Stark apparatus for 17 hours. The mixture was cooled, the solid filtered off and dissolved in the minimum quantity of 5% aqueous 2-dimethylaminoethanol. The solution was filtered, warmed to 60° and acidified with glacial acetic acid and cooled. The solid that crystallised was recrystallised from a mixture of dimethylformamide and ethanol to give brown prisms, m.p. 316—318°, 68%.

The following compound was prepared in a similar manner:
(2) 1-Ethyl-7-hydroxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid m.p. 296—298° from ester of Example 2(11).

EXAMPLE 8

6-Ethoxy-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

Method A

1,4-Dihydro-6-hydroxy-4-oxo-3-quinolinecarboxylic acid (Example 6) (5 g), anhydrous potassium carbonate (16.8 g) and diethyl sulphate (1.34 g) in butanone (500 ml) were stirred and heated under reflux for 20 hours. The solid was filtered off and the filtrate evaporated to give a solid residue of 6-ethoxy-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, ethyl ester, m.p. 98—102.5°, 61%. This ester (3.6 g) was heated with a solution of sodium hydroxide (0.6 g) in water (40 ml) and ethanol (40 ml) for 2 hours. The solution was concentrated to 50 ml and acidified with glacial acetic acid and the precipitated solid was collected, m.p. 192—193°, 91%.

Method B

1-Ethyl-1,4-dihydro-6-hydroxy-4-oxo-3-quinolinecarboxylic acid (Example 7) (4.2 g), potassium carbonate (12.4 g) and diethyl sulphate (7.1 ml) in butanone (420 ml) were stirred and heated under reflux for 16 hours. The solid was filtered off and the filtrate evaporated to give a brown oil which was heated at 80° with aqueous sodium hydroxide (100 ml, 2N) for 45 minutes. The solution obtained was acidified with hydrochloric acid and the solid formed was collected, m.p. 191.5—193°.

The following compound was prepared in a similar manner:
1-Ethyl-1,4-dihydro-7-(2-hydroxyethoxy)-4-oxo-3-quinolinecarboxylic acid, m.p. 229—231°, alkylating agent, 2-bromoethanol from acid of Example 7(2).

EXAMPLE 9

1-(2-Formyloxyethyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

Formic acid (2 ml) was added slowly with stirring to acetic anhydride (4 ml) at 0°. The mixture was heated at 50° for 15 minutes, cooled to 0° and added dropwise to a solution of 1,4-dihydro-1(2-hydroxyethyl)-4-oxo-3-quinolinecarboxylic acid (Example 5) (2.5 g) in dry pyridine (25 ml) at 0°. After 24 hours the precipitated solid was collected, washed with water and dried m.p. 224—226°, 89%.

EXAMPLE 10

(1) 1,4-Dihydro-6-methoxy-4-oxo-N(1H-tetrazol-5-yl)-3-quinolinecarboxamide

1,4-Dihydro-6-methoxy-4-oxo-3-quinolinecarboxylic acid (Example 4(2)) (3.5 g) and N,N'-carbonyldiimidazole (3.9 g) in dry dimethylformamide (35 ml) were heated at 80° for 13 hours. 5-Amino-1H-tetrazole (3.4 g) was added and the mixture was stirred for 45 minutes at 80°. The precipitated solid was filtered off and dissolved in aqueous sodium hydroxide. The solution was acidified with glacial acetic acid and the solid which separated was collected, washed with water and dried, m.p. 338—340°, 77%.

The following compounds were prepared under similar conditions from the corresponding quinolinecarboxylic acids.

(2) 6 - Chloro - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 301—302.5°, 66%, from 6 - chloro - 1,4 - dihydro - 4 - oxo - 3 - quinolinecarboxylic acid.

(3) 1,4 - Dihydro - 6 - nitro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 328—330° from 1,4 - dihydro - 6 - nitro - 4 - oxo - 3 - quinolinecarboxylic acid, 41%.

(4) 1,4-Dihydro-4-oxo-N(1H-tetrazol-5-yl)-7-trifluoromethyl-3-quinolinecarboxamide, m.p. 319—322°, 32%, from 1,4-dihydro-4-oxo-7-trifluoromethyl-3-quinolinecarboxylic acid.

(5) 1,4-Dihydro-8-methoxy-4-oxo-N(1H-tetrazol-5-yl)-3-quinolinecarboxamide, m.p. 345—346°, 7%, from 1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid.

(6) 1,4-Dihydro-4-oxo-N(1H-tetrazol-5-yl)-8-trifluoromethyl-3-quinolinecarboxamide, m.p. 298—299.5° from 1,4-dihydro-4-oxo-8-trifluoromethyl-3-quinolinecarboxylic acid, 53%.

(7) 6-Butyl-1,4-dihydro-4-oxo-N(1H-tetrazol-5-yl)-3-quinolinecarboxamide, m.p. 314° from the corresponding acid (Example 4), 25%.

(8) 1,4 - Dihydro - 6,7 - dimethoxy - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 306° (d) from 1,4 - dihydro - 6,7 - dimethoxy - 4 - oxo - 3 - quinolinecarboxylic acid, 43%.

(9) 6 - Dimethylamino - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 328—329° from 6 - dimethylamino - 1,4 - dihydro - 4 - oxo - 3 - quinolinecarboxylic acid.

(10) 1,4 - Dihydro - 2 - methyl - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 302—305° from 1,4-dihydro-2-methyl-4-oxo-3-quinolinecarboxylic acid.

(11) 1 - Ethyl - 1,4 - dihydro - 6 - isopropyl - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 293—294°, 51%, from the corresponding acid (Example 5(11)).

EXAMPLE 11

(1) 1-Ethyl-1,4-dihydro-4-oxo-N(1H-tetrazol-5-yl)-3-quinolinecarboxamide

1-Ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (31 g) and N,N'-carbonyldiimidazole (23.1 g) were dissolved in dry dimethylformamide (200 ml) and the solution was stirred at 80° for 6 hours. 5-Amino-1H-tetrazole (22 g) was added and the mixture was stirred at 80° for 1 hour. The precipitated solid was collected and dried, m.p. 309—311° (d).

The following compounds were prepared similarly:

(2) 1,4 - Dihydro - 1 - methyl - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 332° from 1,4-dihydro-1-methyl-4-oxo-3-quinolinecarboxylic acid, 32%.

(3) 1 - Allyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 308—309° (d) from the corresponding acid (Example 5(2)), 53%.

(4) 1 - Benzyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. above 277° (d) from the corresponding acid (Example 5(3)), 26%.

(5) 6 - Ethoxy - 1 - ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 312.5—314° (d) from the corresponding acid (Example 8), 43%.

(6) 6 - Butyl - 1 - ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. above 310° (d) from the corresponding acid (Example 5(6)), 53%.

(7) 1 - Ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 7 - trifluoromethyl - 3 - quinolinecarboxamide, m.p. 329—329.5°, from the corresponding acid (Example 5(5)), 71%.

(8) 1,4 - Dihydro - 1(2 - methoxyethyl) - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide m.p. 285—287° from the corresponding acid, (Example 5(10)).

(9) 1 - Ethyl - 7 - fluoro - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 309.5—311.5° from the corresponding acid, (Example 5(8)).

(10) 1 - [2 - (Benzylmethylamino)ethyl] - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 256—259° from the corresponding acid (Example 5 (9)).

EXAMPLE 12

1,4-Dihydro-1-isopropyl-4-oxo-N(1H-tetrazol-5-yl)-3-quinolinecarboxamide

Triethylamine (1.6 ml) was added to 1,4-dihydro-1-isopropyl-4-oxo-3-quinolinecarboxylic acid (Example 5(7)), (2.3 g) in dimethylformamide and the solution was cooled to 0°. Ethyl chloroformate (1.2 ml) was added and the mixture was stirred for 30 minutes. 5-Amino-1H-tetrazole (8.5 g) was added and the mixture was stirred at room temperature for 20 hours. The solid was filtered off and the filtrate was evaporated. The residue was crystallised from dimethylformamide to give the product which had m.p. 305—310° (d).

EXAMPLE 13

1-Ethyl-1,4-dihydro-4-oxo-N(1H-tetrazol-5-yl)-3-quinolinecarboxamide

1-Ethyl-1,4-dihydro-4-oxo-3-quinolinecarbonyl chloride

1-Ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (10.85 g), thionyl chloride (8.75 g) and dimethylformamide (5.4 g) were heated at 100° for 1 hour. The thionyl chloride was removed and dimethylformamide (5 ml) was added and the solid was collected. It had m.p. 185—188°.

1-Ethyl-1,4-dihydro-4-oxo-N(1H-tetrazol-5-yl)-3-quinoline carboxamide

1-Ethyl-1,4-dihydro-4-oxo-3-quinolinecarbonyl chloride (1.2 g) in dry dimethylformamide (30 ml) was cooled to 0° and treated with triethylamine (2 g). 5-Amino-1H-tetrazole (0.6 g) was added and the mixture was warmed to 40—45° and stirred at this temperature for 6 hours and cooled. Water (10 ml) and glacial acetic acid were added and the solid was collected and dried. It had m.p. 316—317°.

EXAMPLE 14

1-Ethyl-1,4-dihydro-4-oxo-N(1H-tetrazol-5-yl)-3-quinolinecarboxamide, sodium salt

1-Ethyl-1,4-dihydro-4-oxo-N(1H-tetrazol-5-yl)-3-quinolinecarboxamide (Example 11) (24 g) was suspended in water (150 ml) and 2N sodium hydroxide was added until a clear solution was just obtained (pH 8.4). The solution was concentrated to 50 ml. and methanol (100 ml) was added. The solid which crystallised was filtered off and dried m.p. above 360°.

EXAMPLE 15

1(2-Dimethylaminoethyl)-1,4-dihydro-4-oxo-N(1H-tetrazol-5-yl)-3-quinolinecarboxamide, hydrochloride, dihydrate

N,N'-Carbonyldiimidazole (1.3 g) was added to a mixture of 1(2-dimethylaminoethyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, hydrochloride (Example 5(4)) (1.5 g) and dry dimethylformamide (30 ml). The solution was stirred and heated to 100° for 5 hours. 5-Amino-1H-tetrazole (0.7 g) was added and heating and stirring continued for a further hour and cooled. The solid was filtered off, dissolved in dilute sodium hydroxide and filtered. The filtrate was warmed to 60° and acidified with dilute hydrochloric acid. The mixture on cooling deposited white crystals which were collected and dried, m.p. 280.5—281.5°, 52%.

EXAMPLE 16

1(2-Formyloxyethyl)-1,4-dihydro-4-oxo-N(1H-tetrazol-5-yl)-3-quinolinecarboxamide

N,N'-Carbonyldiimidazole (1.24 g) and 1 - (2 - formyloxyethyl) - 1,4 - dihydro - 4 - oxo - 3 - quinolinecarboxylic acid (Example 9) (2 g) were added to dry dimethylformamide (40 ml) and the solution was stirred and heated to 100° for 5 hours. 5-Amino-1H-tetrazole (0.65 g) was added and the mixture heated at 100° for 1 hour and cooled. The solid was filtered off and dried, m.p. 289.5—290.5° (d), 61%.

EXAMPLE 17

1,4-Dihydro-1(2-hydroxyethyl)-4-oxo-N(1H-tetrazol-5-yl)-3-quinolinecarboxamide

A solution of 1(2 - formyloxyethyl) - 1,4 - dihydro - 4 - oxo -N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide (Example 16) (0.7 g) and 2N sodium hydroxide (3 ml) was heated on a steam bath for 5 minutes. The hot solution was acidified with 2N hydrochloric acid and the solid which separated was collected and dried, m.p. 298—300° (d), 94%.

EXAMPLE 18

1,4-Dihydro-4-oxo-N(1H-tetrazol-5-yl)-3-quinolinecarboxamide

2-Dimethylaminoethanol (0.3 ml) was added dropwise to a suspension of 1-benzyl-1,4-dihydro-4-oxo-N(1H-tetrazol-5-yl)-3-quinolinecarboxamide (Example 11(4)) (0.8 g) in water (40 ml) until the solid had dissolved. Palladium oxide on charcoal (10%) (0.1 g) was added and the mixture was shaken with hydrogen at room temperature and atmospheric pressure for 4 hours. The catalyst was filtered off and the filtrate warmed to 80° and acidified with glacial acetic acid and cooled. The solid that separated was filtered off and dried, m.p. 320—323°, 97%.

EXAMPLE 19

1,4-Dihydro-4-oxo-1-propyl-N(1H-tetrazol-5-yl)-3-quinolinecarboxamide

2-Dimethylaminoethanol (0.5 ml) was added dropwise to a suspension of 1 - allyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide (Example 11(3)) (1.5 g) in water (30 ml) until the solid had dissolved. Palladium on charcoal (10%) (0.15 g) was added and the mixture was shaken with hydrogen at atmospheric pressure and room temperature for 2 hours and filtered. The filtrate was warmed to 60° and acidified with glacial acetic acid and cooled. The white solid was filtered off and dried, m.p. 298—301° (d), 91%.

EXAMPLE 20

1-Ethyl-1,4-dihydro-7-hydroxy-4-oxo-N(1H-tetrazol-5-yl)-3-quinolinecarboxamide

7 - Benzyloxy - 1 - ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide (Example 22(5)) (0.5 g) in ethanol (20 ml) and water (20 ml) was treated with 2N sodium hydroxide to give a solution pH 9.5. Palladium on charcoal catalyst (100 mg., 10%) was added and the mixture was stirred under hydrogen at room temperature and atmospheric pressure for 18 hours. Further aqueous sodium hydroxide was added to dissolve the solid which had separated and the catalyst was filtered off. The filtrate was acidified with dilute hydrochloric acid and the solid was collected and crystallised from dimethylformamide. The product melted with decomposition at 341°.

EXAMPLE 21

6-Amino-1,4-dihydro-4-oxo-N(1H-tetrazol-5-yl)-3-quinolinecarboxamide

2-Dimethylaminoethanol was added dropwise to 1,4 - dihydro - 6 - nitro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide (1.8 g) (Example 10(3)) in water (50 ml). Palladium oxide on charcoal catalyst (0.2 g., 10%) was added to the clear solution which was then shaken with hydrogen at atmospheric pressure and room temperature for 3 hours. The catalyst was filtered off and the filtrate was evaporated. The residue was crystallised from ethanol to give the product which did not melt below 400°.

EXAMPLE 22

(1) 1 - Ethyl - 1,4 - dihydro - 7 - (2 - methoxyethoxy) - 4 - oxo - N - (1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide

Sodium (0.5 g) was added to 1 - ethyl - 7 - fluoro - 1,4 - dihydro - 4 - oxo - N - 1H - tetrazol - 5 - yl - 3 - quinolinecarboxamide (Example 11(9)) (1.5 g) in 2-

methoxyethanol (25 ml) and the mixture was stirred at 100° for 2 hours. Acetic acid (4 ml) was added, and the mixture was evaporated to dryness. The residue was washed with water, and recrystallised from dimethylformamide, m.p. 294—295° (d), 24%.

The following compounds were prepared in a similar manner:

(2) 1 - Ethyl - 1,4 - dihydro - 7 - (2 - hydroxyethoxy) - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 315° (d), 31%.
(3) 7 - Allyloxy - 1 - ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 297° (d), 32%.
(4) 1 - Ethyl - 1,4 - dihydro - 7 - isopropoxy - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 287° (d), 20%.
(5) 7 - Benzyloxy - 1 - ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 292° (d), 52%.
(6) 7 - (2 - Dimethylaminoethoxy) - 1 - ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 296° (d).
(7) 7 - (2 - Aminoethoxy) - 1 - ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 290° (d).

EXAMPLE 23

(1) 7 - Benzylamino - 1 - ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 -yl) - 3 - quinolinecarboxamide

1 - Ethyl - 7 - fluoro - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide (Example 11(9)) (1.5 g), benzylamine (4.5 g) and water (4.5 g) were heated at 120° for 6 hours. The mixture was acidified to pH 1 with hydrochloric acid, and the solid was recrystallised from dimethylformamide, and had m.p. 304° (d).

The following compounds were prepared in a similar manner:

(2) 1 - Ethyl - 1,4 - dihydro - 7 - (2 - hydroxyethylamino) - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 301° (d).
(3) 1 - Ethyl - 1,4 - dihydro - 7 - morpholino - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 319.5°—320.5° (d).
(4) 1 - Ethyl - 1,4 - dihydro - 7 - (4 - methyl - 1 - piperazinyl) - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, hydrochloride, m.p. 311° (d).
(5) 1 - Ethyl - 1,4 - dihydro - 4 - oxo - 7 - piperidino - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, m.p. 319° (d).

EXAMPLE 24

1,4-Dihydro-1-(2-methylaminoethyl)-4-oxo-N(1H-tetrazol-5-yl)-3-quinolinecarboxamide

1 - [2 - (Benzylmethylamino)ethyl] - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide hydrochloride (Example 11(10)) (1.35 g) and palladium on charcoal catalyst (0.1 g) in acetic acid (50 ml, glacial) were shaken with hydrogen at 60°C and atmospheric pressure. The catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in hot aqueous 2-dimethylaminoethanol and the solution was filtered. Glacial acetic acid was added to the filtrate to give a mixture pH 7.5 and the solid was collected and dried. It had m.p. 307° (d).

EXAMPLE 25

Inhalation aerosol

A formula for an inhalation aerosol is given below. The quantities given are those contained in a metered dose containing 2 mg of active ingredient. The active ingredient is the sodium salt of the compound of Example 14. This may be replaced by any one of the other compounds according to the invention specifically described herein.

Formula

Active ingredient Sodium salt	2.25 mg
Emulsifier YN	0.075 mg
Propellant Arcton 11 (Arcton is a Registered Trade Mark)	23.10 mg
Propellant Arcton 12	59.30 mg

Method

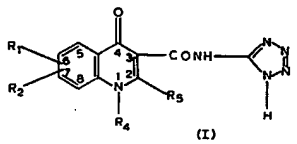
The active ingredient Sodium salt is micronised and mixed with the Arcton 11

together with the Emulsier YN. The required quantity of this suspension is filled into an aerosol can and a suitable metering valve crimped in place. The Arcton 12 is filled into the can through the valve.

Emulsifier YN is supplied by Cadbury Brothers Ltd., Bournville, England.

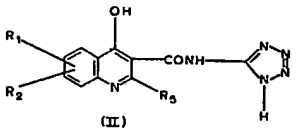
WHAT WE CLAIM IS:—

1. Compounds of the general formula I:



(I)

and tautomers thereof of the general formula II (when R_4=H);



(II)

and pharmaceutically acceptable salts and esters thereof, in which:

R_1 and R_2 which may be the same or different represent a hydrogen atom, a halogen atom, or an alkyl, trifluoromethyl or nitro group, or a group OR_3 in which R_3 represents a hydrogen atom, or an alkenyl or alkyl group, which alkyl group may be substituted by alkoxy, aryl, amino, alkylamino, dialkylamino, hydroxy or acyloxy groups; or a group NR_6R_7 in which R_6 and R_7 which may be the same or different represent a hydrogen atom or an alkyl group, which alkyl group may be substituted with a hydroxy group or acyloxy group or in which R_6 and R_7 together with the nitrogen atom form a 5 or 6 membered ring which may contain additional hetero atoms;

R_4 represents a hydrogen atom, an alkenyl or alkyl group, which alkyl group may be substituted with hydroxy, acyloxy, alkoxy, aryl, amino, alkylamino, dialkylamino or alkylaralkylamino groups; and

R_5 represents a hydrogen atoms or an alkyl group.

2. Compounds as claimed in claim 1 in which R_1 or R_2 represent an alkyl group containing from 1 to 4 carbon atoms, or an alkenyl group containing 3 to 5 carbon atoms or an alkoxy group containing 1 to 4 carbon atoms, or a group within the meaning given in claim 1 containing such group as part thereof.

3. Compounds as claimed in claim 1 or claim 2 in which R_4 represents an alkyl group containing from 1 to 4 carbon atoms or alkenyl group containing from 3 to 5 carbon atoms or a group within the meaning given in claim 1 containing such group as part thereof.

4. Compounds as claimed in any of claims 1 to 3 in which R_5 represents alkyl containing from 1 to 4 carbon atoms.

5. Compounds as claimed in claim 1 in which R_1, R_2, R_4 and R_5 have the following meanings:

R_1 and R_2: hydrogen, chlorine, fluorine, isopropyl, butyl, trifluoromethyl, nitro, hydroxy, methoxy, ethoxy, isopropoxy, allyloxy, 2-hydroxyethoxy, 2-methoxyethoxy, benzyloxy, 2-(dimethylamino)-ethoxy, 2-aminoethoxy, amino, benzylamino, 2-hydroxyethylamino, dimethylamino, morpholino, N-methylpiperazinyl, piperidino;

R_4: hydrogen, methyl, ethyl, propyl, isopropyl, benzyl, allyl, 2-hydroxyethyl, 2-formyloxyethyl, 2-methoxyethyl, 2-(methylamino)ethyl, 2-(dimethylamino)ethyl, 2-(methylbenzylamino)ethyl;

R_5: hydrogen, methyl.

6. 1,4 - Dihydro - 6 - methoxy - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

7. 6 - Chloro - 1,4 - dihydro - 4 - oxo -N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

8. 1,4 - Dihydro - 6 - nitro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

9. 1,4 - Dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 7 - trifluoromethyl - 3 - quinolinecarboxamide.

10. 1,4 - Dihydro - 8 - methoxy - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

11. 1,4 - Dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 8 - trifluoromethyl - 3 - quinolinecarboxamide.

12. 6 - Butyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

13. 1,4 - Dihydro - 6,7 - dimethoxy - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

14. 6 - Dimethylamino - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

15. 1,4 - Dihydro - 2 - methyl - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

16. 1 - Ethyl - 1,4 - dihydro - 6 - isopropyl - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

17. 1 - Ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

18. 1,4 - Dihydro - 1 - methyl - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

19. 1 - Allyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

20. 1 - Benzyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

21. 6 - Ethoxy - 1 - ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

22. 6 - Butyl - 1 - ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

23. 1 - Ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 7 - trifluoromethyl - 3 - quinolinecarboxamide.

24. 1,4 - Dihydro - 1(2 - methoxyethyl) - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

25. 1 - Ethyl - 7 - fluoro - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

26. 1 - [2 - (Benzylmethylamino)ethyl] - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

27. 1,4 - Dihydro - 1 - isopropyl - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

28. 1 - Ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, sodium salt, dihydrate.

29. A compound as claimed in claim 1 which is 1(2 - dimethylaminoethyl) - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide, hydrochloride, dihydrate.

30. 1(2 - Formyloxyethyl) - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

31. 1,4 - Dihydro - 1(2 - hydroxyethyl) - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

32. 1,4 - Dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

33. 1,4 - Dihydro - 4 - oxo - 1 - propyl - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

34. 1 - Ethyl - 1,4 - dihydro - 7 - hydroxy - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

35. 6 - Amino - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

36. 1 - Ethyl - 1,4 - dihydro - 7 - (2 - methoxyethoxy) - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

37. 1 - Ethyl - 1,4 - dihydro - 7 - (2 - hydroxyethoxy) - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

38. 7 - Allyloxy - 1 - ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

39. 1 - Ethyl - 1,4 - dihydro - 7 - isopropoxy - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

40. 7 - Benzyloxy - 1 - ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

41. 7 - (2 - Dimethylaminoethoxy) - 1 - ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

42. 7 - (2 - Aminoethoxy) - 1 - ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

43. 7 - Benzylamino - 1 - ethyl - 1,4 - dihydro - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

44. 1 - Ethyl - 1,4 - dihydro - 7 - (2 - hydroxyethylamino) - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

45. 1 - Ethyl - 1,4 - dihydro - 7 - morpholino - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

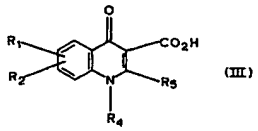
46. 1 - Ethyl - 1,4 - dihydro - 7 - (4 - methyl - 1 - piperazinyl) - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

47. 1,4 - Dihydro - 1 - (2 - methylaminoethyl) - 4 - oxo - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

48. 1 - Ethyl - 1,4 - dihydro - 4 - oxo - 7 - piperidino - N(1H - tetrazol - 5 - yl) - 3 - quinolinecarboxamide.

49. A process for the preparation of compounds as claimed in claim 1 which comprises:

(a) condensing a 1,4-dihydro-4-oxo-3-quinolinecarboxylic acid of the general formula (III):



(III)

or an activated derivative thereof, (in which R_1, R_2, R_4 and R_5 have the meanings given in claim 1) with 5-amino-tetrazole, if desired with subsequent conversion of any of the groups R_1, R_2, R_4 and R_5 into other groups within the meanings given in claim 1;

(b) for the production of compounds claimed in claim 1 in which the group R_1 represents a group OR_3 or a group NR_6R_7 in the 7-position reacting the corresponding compound as claimed in claim 1 in which there is a fluorine atom in the 7 position with an alkoxide XOR_3 in which X is a metal atom and R_3 has the meaning given in claim 1 or with an amine NHR_6R_7 in which R_6 and R_7 have the meanings given above, or

(c) for the production of compounds as claimed in claim 1 in which R_4 is hydrogen or R_1 is hydroxy or a group NHR_6 in which R_6 has the meaning given above by the hydrogenolysis respectively of the corresponding compound claimed in claim 1 in which R_4 is $-CH_2C_6H_5$, or R_1 is $OCH_2C_6H_5$ or $NR_6CH_2C_6H_5$ in which R_6 has the meaning given above; or

(d) for the production of compounds as claimed in claim 1 in which the group R_1 is NH_2, catalytically reducing a compound as claimed in claim 1 in which R_1 is NO_2; or

(e) for the production of compounds as claimed in claim 1 in which R_4 represents hydroxyalkyl, hydrolysing a compound as claimed in claim 1 in which R_4 is acyloxyalkyl, said processes (b) to (e) being carried out independently or as a subsequent conversion of process (a), the product if desired being isolated as a pharmaceutically acceptable salt or being converted from one salt to another.

50. A process as claimed in process (a) of claim 49 in which condensation is effected with N,N'-carbonyl-diimidazole.

51. A process as claimed in process (a) of claim 49 in which an acid halide or mixed anhydride is used as activated derivative of said acid.

52. A process as claimed in claim 49 substantially as herein described with reference to Examples 10—24.

53. Compounds as claimed in claim 1 when prepared by a process as claimed in any of claims 49—52.

54. A pharmaceutical composition comprising a compound as claimed in claim 1 or claim 53 in association with a pharmaceutical carrier or diluent.

55. A composition as claimed in claim 54 in a form suitable for oral administration.

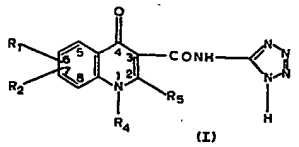
56. A composition as claimed in claim 55 in dosage unit form each unit containing from 2—1500 mg of the active ingredient.

57. A composition as claimed in claim 54 in a form suitable for administration by inhalation.

58. A composition as claimed in claim 57 in dosage unit form, each unit containing from 0.1 to 20 mg of active ingredient.

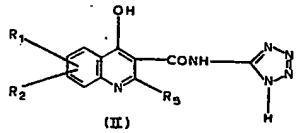
59. A composition as claimed in claim 54 substantially as herein described with reference to Example 25.

60. Compounds of the general formula I:



(I)

and tautomers thereof of the general formula II (when R_4=H);



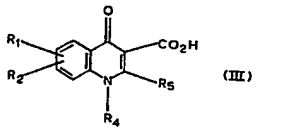
(II)

and pharmaceutically acceptable salts and esters thereof, in which:

R_1 and R_2 which may be the same or different represent a hydrogen atom, a halogen atom, or an alkyl, trifluoromethyl or nitro group, or a group OR_3 in which R_3 represents a hydrogen atom, or an alkenyl group or an alkyl group, which alkyl group may be substituted by alkoxy, aryl, amino, alkylamino, dialkylamino, hydroxy or acyloxy groups; or a group NR_6R_7 in which R_6 and R_7 which may be the same or different represent a hydrogen atom or an alkyl group, which alkyl group may be substituted with a hydroxy group;

R_4 represents a hydrogen atom, an alkenyl or alkyl group, which alkyl group may be substituted with hydroxy, acyloxy, alkoxy, aryl, amino, alkylamino or dialkylamino groups; and R_5 represents a hydrogen atom or an alkyl group.

61. A process for the preparation of compounds as claimed in claim 60 which comprises condensing a 4-oxo-1[H]-quinoline-3-carboxylic acid derivative of the general formula (III):



(III)

or an activated derivative thereof, (in which R_1, R_2, R_4 and R_5 have the meanings given in claim 1) with 5-aminotetrazole, if desired with subsequent conversion of any of the groups R_1, R_2, R_4 and R_5 into other groups within the meanings given in claim 60, the product if desired being isolated as a pharmaceutically acceptable salt.

62. Pharmaceutical compositions comprising a compound as claimed in claim 60 or a compound prepared by the process of claim 61 in association with an inert carrier or diluent.

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